IN THE CLAIMS

For the Examiner's convenience, all pending claims are listed below.

1-62. (Cancelled)

63. (Currently Amended) An isolated antibody which specifically binds to a polypeptide selected from the group consisting of:

a) a polypeptide comprising ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5 , said naturally occurring amino acid sequence having protein kinase activity, and

c) an immunogenic fragment of a polypeptide having ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5.

64. (Currently Amended) The antibody of claim 63 which specifically binds to a polypeptide comprising ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5.

65. (Currently Amended) The antibody of claim 63 which specifically binds to a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5, said naturally occurring amino acid sequence having protein kinase activity.

66. (Withdrawn)A diagnostic test for a condition or disease associated with the expression of PKH in a biological sample, the method comprising:

a) combining the biological sample with an antibody of claim 63, under conditions suitable for the antibody to bind the polypeptide and form an antibody:polypeptide complex, and

b) detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

67. (Previously Presented) The antibody of claim 63, wherein the antibody is:

a) a chimeric antibody,

b) a single chain antibody,

c) a Fab fragment,

d) a $F(ab')_2$ fragment, or

e) a humanized antibody.

68. (Previously Presented) A composition comprising an antibody of claim 63 and an acceptable excipient.

69. (Withdrawn) A method of diagnosing a condition or disease associated with the expression of PKH in a subject, comprising administering to said subject an effective amount of the composition of claim 68.

70. (Previously Presented) A composition of claim 68, wherein the antibody is labeled.

71. (Withdrawn) A method of diagnosing a condition or disease associated with the expression of PKH in a subject, comprising administering to said subject an effective amount of the composition of claim 70.

72. (Withdrawn, Currently Amended) A method of preparing a polyclonal antibody with the specificity of the antibody of claim 63, the method comprising:

a) immunizing an animal with a polypeptide having ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5 or an immunogenic fragment thereof, under conditions to elicit an antibody response,

b) isolating antibodies from said animal, and

c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having ~~an~~ the amino acid sequence of SEQ ID NO:NO:~~1-9~~ 5.

73. (Previously Presented) A polyclonal antibody produced by a method of claim 72.

74. (Previously Presented) A composition comprising the polyclonal antibody of claim 73 and a suitable carrier.

75. (Withdrawn, Currently Amended) A method of making a monoclonal antibody with the specificity of the antibody of claim 63, the method comprising:

a) immunizing an animal with a polypeptide having the amino acid sequence of SEQ ID NO:~~1-9~~ 5 or an immunogenic fragment thereof, under conditions to elicit an antibody response,

b) isolating antibody producing cells from the animal,

c) screening the isolated antibodies with the polypeptide, thereby identifying a monoclonal antibody which binds specifically to a polypeptide having ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5.

76. (Previously Presented) A monoclonal antibody produced by a method of claim 75.

77. (Previously Presented) A composition comprising the monoclonal antibody of claim 76 and a suitable carrier.

78. (Previously Presented) The antibody of claim 63, wherein the antibody is produced by screening a Fab expression library.

79. (Previously Presented) The antibody of claim 63, wherein the antibody is produced by screening a recombinant immunoglobulin library.

80. (Withdrawn, Currently Amended) A method of detecting a polypeptide having ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5 in a sample, the method comprising:

a) incubating the antibody of claim 63 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and

b) detecting specific binding, wherein specific binding indicates the presence of a polypeptide having ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5 in the sample.

81. (Withdrawn, Currently Amended) A method of purifying a polypeptide having ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5 from a sample, the method comprising:

a) incubating the antibody of claim 63 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and

b) separating the antibody from the sample and obtaining the purified polypeptide having ~~an~~ the amino acid sequence of SEQ ID NO:~~1-9~~ 5.

REMARKS

I. Comments regarding the restriction requirement

Claims 66, 69, 71, 72, 75, 80, 81 are "method of use" claims which all depend from the product claim 63. Therefore, upon allowance of product claim 63, the method of use claims 66, 69, 71, 72, 75, 80, 81 should be rejoined and considered together, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products.

II. Rejections for lack of utility under 35 U.S.C. §§101 and 112

Claims 73 has been rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that " the claim is directed to a polyclonol antibody that is not isolated, thus the claim reads on a product of nature. (04/09/03 Office Action, at page 4). This rejection is traversed as it is without basis. Applicants direct the Examiner's attention to independent method claim 72, from which claim 73 depends. Claim 72 recites the following:

> 72. A method of preparing a polyclonal antibody with the specificity of the antibody of claim 63, the method comprising:
> a) immunizing an animal with a polypeptide having an amino acid sequence of SEQ ID NO:5 or an immunogenic fragment thereof, under conditions to elicit an antibody response,
> b) isolating antibodies from said animal, and
> c) screening the **isolated antibodies** with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO:5.

The polyclonol antibodies produced from the method of claim 72 are, is recited in the claim, isolated antibodies; therefore, the claimed antibodies in claim 73 are isolated antibodies. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 63-65, 67, 68, 70, 73, 74 and 76-79 have been rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." In particular the Examiner asserts that "The claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility." (04/09/03 Office Action, at page 4). This rejection is respectfully traversed as it incorrect as a matter of law and as a matter of fact.

At the outset, please note that the instant application is a divisional application of and claims priority to United States Patent Application Serial No. 09/420, 915 filed on 10/20/1999 which was a divisional application of and claims priority to United States Patent Application Serial No. 09/173, 581 filed on 10/15/1998 (hereinafter "the Bandman '581 application"), all having the identical specification (although in some cases the page numbers may not precisely line up). For purposes of consistency, all references to the specification are to that of the Bandman '581 application.

Embodiments of the invention at issue include an antibody that specifically binds to a polypeptide sequence corresponding to a gene that is expressed in human tissue including reproductive, nervous and hematopoetic/immune tissues as determined from cDNA libraries which were constructed from messenger RNA isolated from human placental tissue (See Tables 3 and 4 of the Specification and pages 34-35, Examples I & II). Further, the polypeptide to which the claimed antibodies specifically bind, is demonstrated to be a member of the protein kinase family whose biological functions include catalysis of the phosphorylation of various target proteins by adenosine triphosphate (ATP). (See the Specification, for example, at page 1, lines 11-14). Applicants also enclose a recent BLAST search which provides further evidence that polypeptide recited in the instant claims is indeed a member of the protein kinase family. In particular, the polypeptide having the amino sequence of SEQ ID NO:5 shares 51% sequence identity with a mouse protein kinase (PAPK, GI:15667468). Nishigaki et al. demonstrated PAPK to have protein kinase activity using an immune complex kinase assay. (See Nishigaki K, et al.: Identification and Characterization of a Novel Ste20/Germinal Center Kinase-related Kinase, Polyploidy-associated Protein Kinase. S. J Biol Chem. 2003 Apr 11;278(15):13520-30, Results Section.) Also they indicate GI:15667468 to be a member of a protein

kinase family based on homologies of 52% and 30% to other protein kinases in that family. (See Nishigaki K, et al., Results Section).

Accordingly, the claimed invention (which includes an antibody that specifically binds to a PKH protein demonstrated to be protein kinase) has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide which are specifically bound by the claimed antibodies actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this response the declaration of Mr. Michael Furness[1] (herein after "the Furness Declaration") describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Furness Declaration describes, in particular, how the polypeptides, which are specifically bound by the claimed antibodies, can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 10).

The Office Action does not dispute that the polypeptides, which are specifically bound by the claimed antibodies, can be used in gene and protein expression monitoring applications. Instead, the Office Action contends that the polypeptides which are specifically bound by the claimed antibodies cannot be useful without precise knowledge of their biological functions. However, the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

Further, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the polypeptides, which are specifically bound by the claimed antibodies, in the absence of any knowledge as to the precise function of the protein. The uses of the polypeptides, which are specifically bound by the claimed antibodies, in gene and protein expression monitoring applications are in fact, independent of their precise biological functions.

---

[1]The Furness Declaration included herewith is unexecuted. The executed Declaration and Furness Declaration will be submitted as soon as it is available

The Office Action has further contended that the specification discloses no diseases associated with PKH activity (See 04/09/03 Office Action, at page 6). Applicants respectfully disagree. The Specification discloses, for example, in Table 3, diseases in which PKH activity has been implicated by the expression of mRNA transcripts (encoding for PKH proteins) which were isolated from diseased tissue including reproductive, nervous and hematopoetic/immune tissues. (See the Specification at page 12, lines 1-5; pages 33-34, Examples I & II; and Table 3). These diseases include cancer as well as inflammatory disorders.

I. The Applicable Legal Standard

To meet the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 U.S.P.Q. 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 U.S.P.Q. 689 (1966). As held by the court in a recent case in the Court of Appeals for the Federal Circuit, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 U.S.P.Q. 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 U.S.P.Q.2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 U.S.P.Q.2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 U.S.P.Q. 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 U.S.P.Q. 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. See the M.P.E.P. at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it (See *In re Cortright*, 165 F.3d 1353, 1357, 49 U.S.P.Q.2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995)). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 U.S.P.Q. 288 (CCPA 1974). If, and only if, the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility (See *Brana*, 51 F.3d at 1566). The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Use of the claimed antibodies to PKH in expression profiling, including diagnosis of disorders or diseases characterized by expression of PKH, for

toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The uses of PKH for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Furness Declaration. The claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity. This is sufficient to establish utility for the claimed invention.

As described *supra*, the instant application is a divisional application of and claims priority to United States Patent Application Serial No. 09/420, 915 filed on 10/20/1999 which was a divisional application of and claims priority to United States Patent Application Serial No. 09/173, 581 filed on 10/15/1998 (hereinafter "the Bandman '581 application"), all having the identical specification.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art reading the Bandman '581 application on October 15, 1998 would have understood that application to disclose the claimed antibodies and the polypeptides to which the claimed antibodies specifically bind to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 10-13). Much, but not all, of Mr. Furness' explanation

concerns the use of the claimed antibodies and the polypeptides to which the claimed antibodies specifically bind in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.,* in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 10.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Bandman '581 application, the Wilkins article, and other related pre-October 1998 publications, persons skilled in the art on 10/15/1998 clearly would have understood the Bandman '581 application to disclose the SEQ ID NO:5 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity. . . (Furness Declaration, ¶10.)
>
> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:5 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer as well as inflammatory disorders for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶12.)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference

gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, p. 26).

B. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Mr. Furness in his declaration.

Toxicology testing is used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

The more genes --and, accordingly, the polypeptides they encode-- that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the

original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Office Action failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the instant rejection should be withdrawn regardless of its merit.

C. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility.

Raytheon v. Roper, 220 U.S.P.Q.2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 U.S.P.Q. 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific and substantial" utilities. (See 04/09/03 Office Action, at page 4). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polypeptide is not required to demonstrate utility.

The Patent Examiner's primary rejection of the claimed invention is based on the grounds that, without information as to the precise biological significance of the claimed invention, the claimed invention's utility is not sufficiently specific. (See 04/09/03 Office Action, at page 7). According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would

require, in addition, that the Applicant provided a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Office actions posits, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide or claimed antibody which specifically binds the polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Because the uses of PKH and antibodies which specifically bind PKH in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

The Office Action rejects the claims at issue on the grounds that the use of an invention as a tool for research is not a "substantial" use. (See 4/09/03 Office Action, at page 7) Because this rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be withdrawn.

There is no authority for the proposition that use as a tool for research is not a substantial utility. To the contrary, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility:

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm. (M.P.E.P. § 2107)

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What Applicants are really saying to those in the art is take these steroids, experiment, and

find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the claimed invention is a tool, rather than an object, of research. Further, it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about PKH polypeptides themselves.

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include uses of the claimed antibodies in diagnostic assays (see the Specification, e.g., at page 29, lines 6-13), and drug screening (See the Specification, e.g., at page 37, lines 13-23).

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdrawal the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of non-useful members would fail to meet the utility requirement. (*Montedison*, 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. Thus the Training Materials cannot be applied consistently with the law.

V. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the instant Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

III. Rejections for lack of enablement under 35 U.S.C. § 112, first paragraph.

Claims 63-65, 67, 68, 70, 73, 74 and 76-79 have been rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the Specification allegedly does not provide enablement commensurate in scope with the claims. (See 04/09/03 Office Action, at page 8). This rejection is respectfully traversed.

First, Applicants note that the Examiner has specifically indicated in the rejection that claims 41-43 are "overly broad." *Id.* This rejection is not understood since claims 41-43 have been cancelled. Also, the Examiner has asserted that the Specification does not describe how to make and use

antibodies which specifically bind to "variants" or "fragments" of SEQ ID NO:5. (See 04/09/03 Office Action, at page 8). Such, however, is not the case. Regardless of the Examiner's position, the rejection should not apply to claim 64, since that claim recites an antibody which specifically binds to a polypeptide comprising "the amino acid sequence of SEQ ID NO:5", and not "fragments" or "variants" of SEQ ID NO:5.

At the outset, the use of the antibodies which specifically bind the recited "variants" and fragments of SEQ ID NO:5 should not be at issue. That is, these antibodies have the same uses as an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:5. For example, the skilled artisan could use the claimed antibodies to purify a protein having an amino acid sequence comprising a variant sequence of SEQ ID NO:5 (See the Specification, for example, at page 41, lines 22-32). In another use, antibodies to variants of the amino acid sequence of SEQ ID NO:5 can be used for drug screening purposes (See the Specification, for example, at page 33, lines 20-23). Note lines 22-23, which state that "antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PKH." Additionally, antibodies which specifically bind to variants of SEQ ID NO:5 can be used, for example, in 2D-PAGE analysis for expression profiling related to toxicology testing, drug discovery and disease diagnosis. Thus, Applicants submit that the skilled artisan would readily know how to use antibodies to a "variant" of the sequence of SEQ ID NO: 5 and that undue experimentation would not be required.

Moreover, there should be no issue with how to make the antibodies *per se*. Methods for making antibodies are well known in the art, and are also described in the Specification at, for example, page 41, lines 6-21. The same methods for producing antibodies to polypeptides which comprise SEQ ID NO:5 could be used to make antibodies which specifically bind "variants" or fragments of SEQ ID NO:5 .

Thus, the rejection appears to based on the presumption that one could not make the claimed antibodies because one would allegedly not be able to make the recited "variants" or "fragments" of SEQ ID NO:5 *per se*, which in turn are used to produce antibodies which specifically bind those proteins. However, this presumption is incorrect.

Note that claim 63 recites not only that the variant polypeptides are at least 90% identical to SEQ ID NO:5 , but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:5 (the amino acid sequences of PKH) and SEQ ID NO:14 (the polynucleotide sequence encoding PKH), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5 ." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. For example:

> In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding PKH or closely related molecules may be used to identify nucleic acid sequences which encode PKH. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding PKH, allelic variants, or related sequences.. (Specification at page 29, lines 28-34)

> Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the PKH encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO: 10-18 or from genomic sequences including promoters, enhancers, and introns of the PKH gene. (Specification at page 30, line 35 to page 31, line 2)

> See also Example V of the Specification, at page 38.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:5. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain variant polynucleotides of SEQ ID NO:14 which, in turn, will allow one to make the

variant polypeptides of SEQ ID NO:5 recited by the present claims. Conventional methods for making antibodies, such as those described in Example XII of the Specification at page 41, can be used to make antibodies which specifically bind to the recited polypeptide variants.

Accordingly, the Voet et al. reference cited by the Examiner, which relates to structure-function relationships in protein, is not pertinent to whether one can make and use the polypeptide variants to which the claimed antibodies specifically bind. That is, regardless of the precise functional characteristics of the SEQ ID NO:5 variants, one can still make those polypeptide variants, and antibodies which specifically bind to the variants, using the disclosure provided by the present specification. These antibodies could then be used, for example, in diagnostic testing, drug discovery, expression profiling, etc.

The rejection's reliance on the Voet et reference is also legally misplaced. The Examiner uses this reference to make the proposition that the function of PKH is not predictable because a single amino acid change in a protein can result in distinct biological activities. (See the 04/09/03 Office Action, at page 9). However, this proposition lacks proper evidentiary relevance. As the court stated in *Boehringer Ingelheim Vetmedica Inc. v. Schering-plough Corporation*, the "fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all." *Boehringer Ingelheim Vetmedica Inc. v. Schering-Plough Corp.*, 320 F.3d 1339,1351 (Fed. Cir. 2003). Here, the Examiner presents no evidence whatsoever of the effect that even a single amino acid change would have on the function of the claimed antibodies.

The Examiner's attention is also directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

Claim 63 recites, *inter alia*, antibodies which specifically bind to "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5 ." In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as PKH-like proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:5 . The "90% variants" recited by the present claims have a variation that is far less than that of all potential PKH-like proteins related to SEQ ID NO:5 , i.e., those PKH-like proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:5 . Therefore, one would expect the SEQ ID NO:5 variants recited by the present claims to have the functional activities of a PKH-like protein.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 ***requires nothing more than objective enablement.*** [emphasis added] How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited antibodies which specifically bind to the recited "variants" and fragments of SEQ ID NO:5 . Hence, a *prima facie* case for non-enablement has not been established with respect to the claimed antibodies which specifically bind to the recited "variants" and fragments of SEQ ID NO:5 . For at least the reasons above, Applicants request withdrawal of the rejection.

IV Rejection for lack of written description under 35 U.S.C. § 112, first paragraph

Claims 63-65, 67, 68, 70, 73, 74 and 76-79 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the

application was filed, had possession of the claimed invention. (See 04/09/03 Office Action, at page 10). In particular, the Office Action alleges that the Specficiation does not provide an adequate written description of antibodies which specifically bind "fragments" or "variants"of SEQ ID NO:5. This rejection is improper, as the claims define subject matter which is described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed subject matter at the time the application was filed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*
> *Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991)

The Examiner's attention is also directed to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of the claimed antibodies which specifically bind to the recited "variants" and "fragments" of SEQ ID NO:5.

The subject matter encompassed by claims 63-65, 67, 68, 70, 73, 74 and 76-79 is either disclosed by the Specification or is conventional or well known to one skilled in the art.

At the outset, note that this rejection should not apply to claim 64. That is, claim 64 defines an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:5 . Thus, this claim does not pertain to the "fragment" and "variant" subject mater to which the Examiner objects.

First note that the "variant" language of independent claim 63 recites a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5." The amino acid sequence of SEQ ID NO:5 is explicitly disclosed in the specification. (See, for example, the Sequence Listing of the Specification). Variants of SEQ ID NO:5 are described in the Specification at, for example, page 2, lines 25-31; page 12, lines 16-19; and page 16, lines 7-9. Fragments of SEQ ID NO:5, including immunogenic fragments, are described in the Specification at, for example, page 2, lines 19-24; page 3, lines, 17-18 and 27-29; page 5, lines 32-35; and page 20, lines 30-34.

One of ordinary skill in the art would recognize polypeptide sequences which are variants having a polypeptide sequence at least 90% identical to SEQ ID NO:5. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant or fragment of SEQ ID NO:5. Accordingly, the specification provides an adequate written description of the recited polypeptide variants and fragments of SEQ ID NO:5. Moreover, the Specification describes antibodies which specifically bind the SEQ ID NO:5 polypeptides. (See the Specification, for example, at pages 22, lines 25-28; and page 29, lines 6-12.)

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and antibodies which specifically bind the proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast

interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define the polypeptides bound by the claimed antibodies in terms of chemical structure, rather than functional characteristics alone. For example, the language of independent claim 63, includes the recitation of chemical structure to define the claimed genus:

> 63. An isolated antibody which specifically binds to a polypeptide selected from the group consisting of:
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 5,
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 5, said naturally occurring amino acid sequence having protein kinase activity, and
> c) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:NO: 5.

From the above it is readily apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:5. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides specifically bound by the claimed antibodies, although the recitation of functional characteristics ("protein kinase activity" and immunogenic") adds to the characterization of the recited "variants" and "fragments" of SEQ ID NO:5. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base his written description inquiry "on whatever is now claimed," the Examiner failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

The Office Actions bases its written description rejection on the contention that the claims cover a "highly variant" genus. (See 04/09/03 Office Action, at page 11). This contention is in error, the

claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the genus of polypeptides recited by the claims is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

Embodiments of the present invention are directed, *inter alia*, to antibodies which specifically bind PKH related proteins, including PKH proteins related to the amino acid sequence of SEQ ID NO:5. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as PKH proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:5. The "variant language" of the present claims recites antibodies which specifically bind a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5" (note that SEQ ID NO:5 has 327 amino acid residues). This variation is far less than that of all potential PKH proteins related to SEQ ID NO:5, i.e., those PKH proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:5.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an

Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of October 15, 1998. Much has happened in the development of recombinant DNA technology in the 19 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:5, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed antibodies that bind specifically to "variants" and "fragments" of SEQ ID NO:5 at the time of filing of this application.

4. Summary

The Examiner failed to base his written description inquiry "on whatever is now claimed." Consequently, the Examiner did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:5. The courts have stressed that structural features are important factors to consider in a written description analysis of claims reciting nucleic acids and proteins. In addition, the genus of polypeptides recited by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the Specification provides an adequate written description of the polypeptide "variants and fragments" recited by the claims, and antibodies which

specifically bind those polypeptides. Accordingly, Applicants respectfully request that the rejection should be withdrawn.

IV Rejection under 35 U.S.C. § 112, second paragraph

Claims 63-65, 67, 68, 70, 73, 74 and 76-79 have been rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that the claims are "indefinite for failing to particular point out and distinctly claim the subject matter which the applicants regards as the invention" (4/09/03, Office Action, at page 13). In particular, the office action contends that claims 63 and 65 are indefinite in the recitation of the term "naturally occurring." *Id.* Applicants respectfully traverse this rejection.

At the outset, it is noted that this rejection should not apply to claim 64, since that claim does not encompass antibodies which specifically bind to the recited "variants" of SEQ ID NO:5.

That is, the recitation of "naturally occurring amino acid sequence" in Claims 63 and 65 defines **where to find** the amino acid sequences encompassed by the claim. The use of the term "naturally-occurring" distinguishes an amino acid that occurs in nature from synthetic or engineered amino acid sequences that are created through manual genetic manipulations. The term "naturally occurring amino acid sequence" thus defines the origin of the amino acid sequence (i.e., even though one could theoretically make the amino acids having at least 90% sequence identity to SEQ ID NO:5 in the laboratory by randomly mutating the SEQ ID NO:5 sequence, the recited "naturally occurring amino acid sequence" must be one that is found in nature). Applicants note that the origin of the amino acid sequence of the recited amino acid is what is defined by "naturally-occurring" and not the amino acid itself. One skilled in the art would understand the meaning of the term "naturally occurring amino acid sequence" within the context of Claims 63 and 65. Moreover, this is standard claim language in claims drawn to polypeptides and amino acids, and its use in the instant Claims 63 and 65 is entirely consistent with its use in numerous issued U.S. patents, including those of the assignee Incyte as well as in patents of others.

Accordingly, withdrawal of the rejection is believed to be in order.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants formally petition for a two month extension of time for reply. Please charge the required fee and any other fee including extension of time fees under 37 CFR § 1.17 to Deposit Account No. **09-0108**.

Respectfully submitted,

INCYTE CORPORATION

Date: 09 September 2003

Richard C. Ekstrom
Reg. No. 37,027
Direct Dial Telephone: (650) 843-7352

Date: 09/09/03

Joel Harris
Reg. No. 44,743
Direct Dial Telephone: (650) 845-4866

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886